Affix Patient Label Here

Division of Pediatric Endocrinology
University Of Minnesota Masonic Children's Hospital

Prevention of Bone Loss After Pediatric Hematopoietic Cell Transplantation

Principal Investigator: Kyriakie Sarafoglou, MD

CONSENT FORM

You are invited to participate in a research study looking at the prevention of bone loss (low bone mineral density) after a marrow or blood stem cell transplant. You are a possible participant in the study because you are being considered for a transplant for a blood disease, metabolic disease, or cancer of the blood or lymph nodes.

Taking part in any clinical research involves risks and may provide some benefits. You need to understand these risks and benefits to make an informed decision about whether or not to be in this study. If it has not occurred, participation in this study (or not) will not affect or change the transplant procedure.

This form is called a consent form. The intent of this form is to let you know the purpose of this study, the treatment plan, and the possible risks and benefits of participation. If you wish to take part in this study, you will be asked to sign this consent form.

Kyriakie Sarafoglou, MD of the University Of Minnesota Division Of Pediatric Endocrinology is the principal investigator (the physician in charge) of this study.

This study is being conducted at the University of Minnesota Masonic Children's Hospital and Seattle Children's Hospital; however the University Of Minnesota is the lead institution and Dr. Sarafoglou is Principal Investigator for entire study.

It is funded by the National Institutes of Health (NIH).

Introduction

Low bone mineral density is common in children and young adults who have bone marrow transplants. Low bone mineral density may increase the risk of early osteoporosis, or weakening of the bones, and broken bones.

Pamidronate is a drug that can increase bone mineral density and has been approved by the Food and Drug Administration (FDA) for use in adults for the treatment of certain conditions that weaken bones in cancer patients and patients with a bone disease called Paget's disease. It has not been approved for use in children or adults receiving bone marrow transplants, but has been used to treat patients with low bone mineral density after transplantation in research studies like this one. This study is being conducted with permission from the United States Food and Drug Administration (FDA).

This study is looking at whether treating children and young adults with pamidronate for the first year after a bone marrow transplant will prevent low bone mineral density. In this study all participants will receive vitamin D and calcium supplements to keep their blood levels at the recommended daily allowance (RDA) for bone health. Supplementation begins upon study entry and continues for 1 year. In addition, approximately 3 months after the transplant, participants will be randomly assigned to either continue supplementation alone or to continue supplementation and receive a dose of pamidronate once every 3 months for three doses (at 3, 6, and 9 months after transplant).

Study Purpose

The purpose of this study is to compare bone mineral density 1 year after transplant in children and young adults who received vitamin D and calcium supplements to keep their blood levels at good levels for bone health to children and young adults who received vitamin D and calcium supplements plus three dose of pamidronate.

Up to 96 persons between 1 and 20 years of age at the time of the transplant will be enrolled into this study with approximately half enrolled through the University of Minnesota (48 persons) and half enrolled through Seattle's Children Hospital.

Study Procedures

If you agree to be in this study the following will occur

During the Pre-Transplant Work-Up:

During the pre-transplant work-up period the following additional tests and procedures will be done for this study:

Pre-Transplant Procedures Done as Part of the Research

- A physical exam and assessment of puberty development (breast development, presence of pubic hair), height and weight

- Dual energy X-ray absorptiometry (DXA) scan of the lower back and body to measure body composition (amount of muscle and fat) and bone density – this will require you to lie on a table for about 15 minutes during the scanning procedure. If you are not able to lie still, mild sedation may be an option.
- Blood (approximately 2 1/2 teaspoons) and urine collected
- Completion of two questionnaires regarding your diet and activity.
- Begin vitamin D, and if needed, calcium supplements continuing once a day for 1 year

Pre-Transplant Procedures That are Part of Standard Treatment

- Pregnancy test if you are female

Once a Week for 3 Weeks after the Transplant (Day 7, Day, 14 and Day 21)

- Blood (approximately 1 ½ teaspoons) and urine collected for research purposes
- A member of the study team will assess you for changes in your health about 1 week and 3 weeks (Day 7 and Day 21) after the transplant

Three Months after the Transplant (Day 90 Follow-Up)

You will be scheduled for a 3 month (Day 90) post-transplant follow-up visit. In addition to the routine post-transplant tests and procedures the following extra tests will be done for this study:

- weight
- Blood (approximately 2 1/2 teaspoons) and urine collected for research purposes
- Repeat pregnancy test for females which must be negative to continue on the study
- Completion of two questionnaires regarding your diet and activity
- Review of vitamin D, and if needed, calcium supplements
- DXA scan, as before, of the lower back and body
- Quantitative peripheral computed tomography (pQCT) scan of one of your forearms and the shin of one leg to look at the strength and density of these bones requiring you to put an arm or leg on the scanner table for approximately 5 minutes of scanning.

At this visit, a brief review of continuing eligibility will be done by the research staff. You must have adequate kidney function and an acceptable Vitamin D level (both determined by a routine blood tests) and not be pregnant to safely be considered for receiving pamidronate.

If you continue to be eligible for this study, you will be randomly assigned to either:

1) continue on the supplements alone or

2) continue on the supplements and receive pamidronate once every 3 months (beginning with this visit) for 3 doses. Pamidronate is given as a 4 to 5 hour intravenous (into a vein) infusion and requires routine lab work to be done ideally the following morning, but may be done within 7 days after the infusion. You will have a brief assessment for side effects before each dose of pamidronate and again approximately 1 week later by telephone.

If you are **not** eligible for randomization, your doctor will discuss the risks and benefits of continuing supplements without being in this study. You will be discontinued from the study and none of the research related procedures or study related compensation would be continued beyond the Day 90 randomization visit. However, we would like to continue to review your medical record after each post-transplant follow-up through one year (Day 360) as if you were still part of the study. This information would be used as part of the study analysis and would be treated in a confidential manner as all study data is handled. If you do not agree to the ongoing review of your medical record you may withdraw your consent at the Day 90 visit or anytime afterwards. Information collected before the withdrawal of consent would still be used for the study.

Six Months after the Transplant (Day 180 Follow-Up)

You will be scheduled for a 6 month (Day 180) post-transplant follow-up visit. In addition to the routine post-transplant tests and procedures the following extra tests will be done for this study:

- weight
- Blood (approximately 2 1/2 teaspoons) and urine collected for research purposes
- Repeat pregnancy test for females only if assigned to pamidronate
- Completion of two questionnaires regarding your diet and activity
- Review of vitamin D, and if needed, calcium supplements
- If you are assigned to the pamidronate group, you will receive an infusion identical to the Day 90 with follow-up lab work as before

Nine Months after the Transplant (Day 270)

If you are doing well after your transplant, follow-up at 9 months is not a required visit. In other words, this visit may be only for the purposes of the research study and for this reason, your costs for travel (gas and meals) will be reimbursed up to a set limit. At this visit, the following will occur:

- weight
- Routine blood (approximately 1 teaspoon) work

- Repeat pregnancy test for females only if assigned to pamidronate
- Completion of two questionnaires regarding your diet and activity
- Review of vitamin D, and if needed, calcium supplements
- If you are assigned to the pamidronate group, you will receive an infusion identical to the Day 90 with follow-up lab work as before

Twelve Months after the Transplant (Day 360)

You will be scheduled for a 12 month (Day 360) post-transplant follow-up visit. This is the last study visit. In addition to the routine post-transplant tests and procedures the following extra tests will be done for this study:

- A physical exam and assessment of puberty development (breast development, presence of pubic hair), height and weight
- Blood (approximately 1 1/2 teaspoons) and urine collected for research purposes
- Repeat pregnancy test for females which must be negative to have the final DXA and pQCT scans
- Completion of two questionnaires regarding your diet and activity
- Review of vitamin D, and if needed, calcium supplements
- DXA scan, as before, of the lower back and body
- pQCT scan of one of your forearms and the shin of one leg

Research Related Testing

Blood and urine will be collected as described in each visit for research related testing.

The samples will be divided up and two types of testing will be done:

- testing right away in the hospital laboratory as any other test ordered for medical care, but the test costs will be paid for by research funds or
- batch testing at the end of the study in a research laboratory using samples from all participants and from all time point that have been stored frozen

The frozen samples will be labeled with an indirect identifier (a unique code assigned to you at study enrollment) so that anyone looking at the sample will not know it belongs to you. A link between the code and your name and other identifying information will be kept in a secure database. The testing will be done in the study's research laboratory at the University Of Minnesota. Any leftover samples will be destroyed once study related testing is completed and

the results are verified. There will be no charge to you or your health plan/insurance for this testing nor will the results be placed in your medical record.

Length of Study Participation

Study participation is from the pre-transplant visit through the first year after the transplant ending at the Day 360 post-transplant follow-up visit unless one of the following occurs:

- you decide to withdraw from study
- you cannot comply with the study expectations
- you become pregnant
- the disease treated by the transplant returns (relapses)
- the study doctor feels continued participation is not in your best interest

If you are assigned to pamidronate, it may be discontinued for the following reasons but continuation of the vitamin D, and if needed, calcium, would be requested until the 1 year post-transplant:

- you refuse further infusions
- a very low calcium blood level
- unacceptable side effects from pamidronate
- the study doctor feels continued pamidronate infusions are not in your best interest
- the disease treated by the transplant returns (relapses)
- the study ends early

If you discontinue the study before 1 year, routine follow-up information (primarily test and procedure results) will continue to be collected from your medical record through your 12 month (Day 360) post-transplant follow-up visit unless you are withdrawing consent. If you do not return to this institution at the above time points, you may be contacted by mail or telephone for a brief update on your health.

Risks of Study Participation

While on study, you may experience all, some, or none of the risks described below. We will work with you to lessen the risks whenever possible.

Assessment of Development

During the physical exam, a study doctor will look at your breasts (if you are a female) and pubic hair to determine sexual development (puberty). This may embarrass you or make you feel uncomfortable. You may refuse this part of the examination.

Blood Draws
There may be a risk for temporary pain, lightheadedness, bruising, bleeding, or infection with any blood draws.

Completion of Study Related Questionnaires
The risks of completing the questionnaires may include feelings of sadness due to inability to have an active lifestyle and/or good food intake. You have the right to refuse to complete any questions that make you uncomfortable. You also may refuse to complete one or more of the questionnaires.

DXA and pQCT scans
As part of the study you will have three DXA scans and two pQCT scans over the course of 1 year. Both types of scan use extremely low energy x-rays. The amount of radiation received from each DXA and pQCT scan is less than the amount you would receive in 1 day from the natural background radiation here in Minnesota. If you are given sedation, the minor side effects of sedation include nausea, vomiting, mild allergic reactions, headache and dizziness.

Pamidronate (if assigned to pamidronate)
A small tube will be placed into a vein for the infusion. There is a risk for temporary pain, bruising, bleeding, clotting, or infection with placement of the intravenous (IV) line. If you have vein access (a catheter or central line) in place, this may be used for the infusion.

The most common (>30%) side effects in adults receiving pamidronate are:

- flu like symptoms

Less common side effects (occurring in <10%) of adults receiving pamidronate:

- high blood pressure
- pain or skin reaction at the IV site
- low levels of calcium, potassium, magnesium, and phosphate in the blood
- loss of appetite
- nausea
- vomiting
- anemia
- urinary tract infection
- cough
- shortness of breath

- feeling tired or uncomfortable

The following are rare (<5%) risks of pamidronate

- A small number of patients that took pamidronate had a side effect called "uveitis" (inflammation of the eye), which causes blurred vision, eye pain, redness, sensitivity to light, and/or irregular pupils.

- A small number of adults that took pamidronate had serious side effects. These were damage to the jawbone; seizures; and kidney damage. Jaw bone damage was more common in cancer patients, if you have cancer, you should practice good oral hygiene to help lessen this risk.

When pamidronate has been given to children as part of studies like this one, the most common side effect has been low levels of calcium in the blood. Some children have had fever, headache, nausea, vomiting, rash, fast heartbeat, and muscle or bone pain the first time they were treated with pamidronate.

Doctors believe that it is possible to have side effects a long time after pamidronate treatment. These potential side effects are abnormally dense bones, broken bones, delayed healing after surgery on bones, esophageal cancer, and damage to the jaw bone. However, these side effects have not been reported after receiving 3 doses of pamidronate.

Other risks of pamidronate have been identified that are rare or apply only to groups of people not participating in this research study. If you wish to learn more about these risks, your doctor can show you a drug package insert or direct you to reliable internet sites with detailed information.

Risks to an Unborn Baby:
Because of low level radiation associated with the scans in this study, a negative pregnancy test is required for all females before a scan is done.

In addition, a negative pregnancy test is required for all females before each dose of pamidronate as the use of pamidronate during pregnancy is not permitted. In addition, to prevent pregnancy, any female who has begun menstruating will be placed on oral contraception for the duration of pamidronate treatment.

For more information about risks and side effects, ask your study doctor.

Benefits of Study Participation

As a study participant, you will have close monitoring of your calcium and vitamin D levels as part of the lab tests being done during the study. This allows the study doctors to detect low levels and provide calcium and vitamin D supplements that may help prevent low bone mineral density.

If the study treatment is successful, children and young adults who received pamidronate may have higher bone mineral density than if they had not been on study and be at lower risk of fractures.

If at the end of the study your bone density is low you and your doctors will be provided that information so that appropriate treatment is given.

The knowledge gained from the study may advance the understanding of bone weakening following bone marrow or blood stem cell transplants and influence future treatment of all children and young adults undergoing a transplant.

Alternatives to Study Participation

You may refuse to take part in this study. You may receive vitamin D and calcium supplements without being on this study. Your doctors can tell you more about the risks and benefits of vitamin D and calcium supplementation independent of this study.

Your decision either way will not affect the plans for the transplant.

Study Costs and Compensation

All tests and procedures associated with research will be paid for by study funds including the collection and testing of all research related blood and urine samples; the cost of the DXA scans at study entry, Day 90 and Day 360; and the cost of the pQCT at Day 90 and Day 360. If you are assigned to receive pamidronate, the cost of the drug and the follow-up labs will be covered by study funds.

You and your insurance carrier will be responsible for all other costs associated with the transplant procedure, including routine diagnostic tests, the preparative regimen given before the

transplant, actual infusion of pamidronate (but not the cost of the drug itself), hospitalizations and follow-up clinic visits. You and your insurance provider (or Medicaid, etc.) will be responsible for payment of all fees and charges related to medical services not covered as a part of the research therapy as well as any co-payments and/or deductibles.

You will receive no monetary compensation for participation in this study other than what is described in the next section.

Compensation for Study Participation

All Participants:

- A maximum of $150 will be compensated for all participants who complete study participation through 1-year. A $50 gift card will be given at the following timepoints as they are completed: Study enrollment, Day 90, and Day 360 visits to partially compensate for the extra time required for study related tests and procedures on days of routine transplant associated visits.

- On Day 270, travel expenses and meals will be reimbursed expenses including up to a set limit as this visit does not routinely coincide with a post-transplant follow-up visit.

Participants Assigned to Pamidronate:
Reimbursement for expenses (lodging, meals) will be offered to patients assigned to pamidronate at Day 180 and 270 visits for an overnight stay (up to $200 for hotel/parking) and meals (up to $50) in order to obtain the study related lab work the next morning..

Reimbursement will be by check mailed to you after documentation of expenses is provided (such as itemized receipts). Mileage will be reimbursed based on the current IRS per mile rate using a "Google" map to estimate the distance between the participant's home address and the University of Minnesota Masonic Children's Hospital.

The Study Coordinator will help with the reimbursement process.

Research Related Injury
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed

in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Confidentiality

The records of this study will be kept private. Information will be kept in your medical record and in study case report forms. Information gained from this study will be used for research and educational purposes. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Departments at the University of Minnesota with regulatory oversight
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

To this extent, confidentiality is not absolute.

If you decide to participate in this study, private health information will be added and stored in a computer database at the Masonic Cancer Center of University of Minnesota. This information will includes your name and medical record number, date of birth, diagnosis, race/ethnicity, and information about your participation in this study. The purpose of storing this information is to assist the Cancer Center in creating reports about research and in making sure that research studies are being done correctly. Your information will not be used for any other purpose. There are no plans to erase information from the database. It will be stored indefinitely at the Masonic Cancer Center.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the Web site will include a summary of the results. You may search this Web site at any time.'

Certificate of Confidentiality

To help protect your privacy, the National Institutes of Health has granted a Certificate of Confidentiality. The researchers can use this Certificate legally to refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the

Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate does not prevent a researcher from reporting information learned in research when required by other state or federal laws, such as mandatory reports to local health authorities for abuse or neglect of children/vulnerable adults, or information to the Food and Drug Administration (FDA) when required in an FDA audit. However, the Certificate limits the researcher from disclosing such information in follow up civil, criminal, legislative or administrative legal proceedings if the information was created or compiled for purposes of the research.

You also should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

Protected Health Information (PHI)

Your protected health information (PHI) created or received for the purposes of this study are protected under the federal regulation known as HIPAA. You will be asked to review and sign a separate HIPAA authorization concerning the use of this information.

Voluntary Participation

Taking part in this study is your choice. You may choose either to take part in the study or not.

You also have the right to withdraw from the study at any time, even after signing the consent form, without giving a reason.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study requirements; or if the study is stopped.

No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You may still get your medical care from this institution.

New Information

You will be told about new information or changes in the study that may affect your health or your willingness to continue in the study.

Contacts and Questions

The physicians involved in your care are available to answer any questions you may have concerning this study. You are encouraged to ask questions now as well as ones that you may have in the future. If you have any questions concerning this study, you also may contact the principal investigator Kyriakie Sarafoglou, MD at (612) 624-5409.

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

You will be given a signed copy of this form to keep for your records.

Affix Patient Label Here

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

_____

Name of participant

_____ _____

Signature of participant Date of signature

_____

Name of person conducting consent process

_____ _____

Signature of person conducting consent process Date of signature